Depression, Anxiety, and the Cardiovascular System: The Psychiatrist's Perspective

Steven P. Roose, M.D.

It is becoming clear that the comorbidity of depression and cardiovascular disease does not occur by chance but rather is an inevitable consequence of the relationship between the conditions. Depression in patients with cardiovascular disease is a significant risk factor for developing symptomatic and fatal ischemic heart disease. Moreover, depressed patients have a higher than expected rate of sudden cardiovascular death. Therefore, appropriate treatment of patients with depression and cardiovascular disease cannot be restricted to considerations of either depression or cardiovascular disease in isolation. The tricyclic antidepressants (TCAs) have various effects on the cardiovascular system, including Type IA antiarrhythmic activity that has been associated with an increased risk of mortality in post–myocardial infarction patients. The selective serotonin reuptake inhibitors (SSRIs) are not associated with adverse cardiac effects. The SSRI paroxetine was compared with a therapeutic level of the TCA nortriptyline in a randomized, controlled study and demonstrated a benign cardiovascular profile, while the TCA induced a significantly higher rate of serious adverse cardiovascular events. On the basis of this favorable cardiovascular profile, the SSRIs should therefore be the preferred choice for the treatment of most patients with comorbid depression and cardiovascular disease. Investigation of putative pathophysiologic mechanisms linking depression and cardiovascular mortality, such as the role of platelet activation, will form the basis for further investigation of antidepressant treatments in order to establish if the antidepressants have a beneficial effect on the prognosis of cardiovascular diseases.   (J Clin Psychiatry 2001;62[suppl 8]:19–22)

It is becoming clear that the comorbidity of depression and cardiovascular disease does not occur by chance but rather is an inevitable consequence of the combined conditions. Studies have indicated a higher than expected incidence of major depression in patients who have either angiographic evidence of cardiovascular disease or have experienced a myocardial infarction (MI) up to 10 days previously.[1,2] Post-MI patients have an incidence of 18% for meeting the criteria for major depression and an incidence of 27% for having significant depressive symptoms.[2] In a 1-year follow-up of patients with documented coronary artery disease (CAD), Carney et al.[3] showed that major depressive disorder is an important independent risk factor for the occurrence of major cardiac events. Therefore, depression could be considered a risk factor for cardiovascular morbidity and mortality to be viewed in addition to other factors such as elevated cholesterol, hypertension, and obesity. As pathophysiologic models are developed, it seems that depression and cardiovascular disease should no longer be considered 2 discrete conditions that can occur parallel to each other—rather, they interact at both an etiologic and a phenomenological level. Furthermore, management of cardiovascular patients with depression would be improved by considering the effect of treatment interventions on both conditions concomitantly.

DEPRESSION AND SYMPTOMATIC AND FATAL ISCHEMIC HEART DISEASE

It is a long-standing and well-replicated observation that depressed patients have a higher rate of sudden cardiovascular death than the general population. In the 1930s, before somatic treatments were available, Malzberg[4] compared the mortality of patients with melancholia with age-matched cohorts in the general population. In every age group, there was a significant increase in mortality attributable to sudden cardiovascular death in melancholic patients compared with the general population (Figure 1). This finding has been replicated in both the United States and Europe.[5–8]

Depression in early life can also be a predictor of the development of symptomatic and fatal ischemic heart disease. The Glostrup study conducted in Scandinavia[9] followed 730 individuals with or without depression over 27
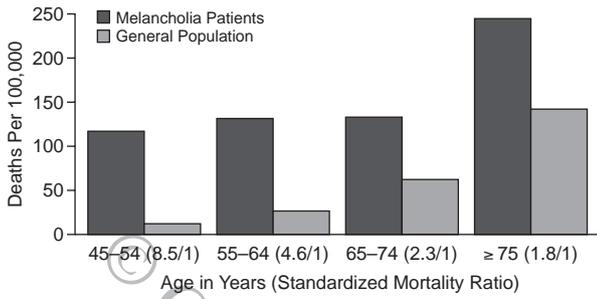
Steven P. Roose

Figure 1. Death Rates in Involutional Melancholia Compared With the General Population, 1929–1931[a]

aReprinted from Malzburg,[4] with permission.

Figure 2. Relative Risk of Acute Myocardial Infarction and Total Cardiovascular Mortality in 730 Individuals With or Without Depression Over 27 Years[a]

aReprinted from Barefoot and Schroll,[9] with permission. Abbreviation: CI = confidence interval.
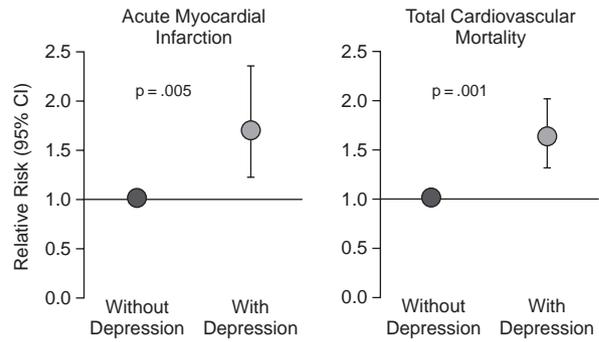
years. Individuals with a history of cardiac disease within 2 years of entering the study were excluded. Over the course of 27 years, there was a higher rate of both symptomatic ischemic disease and total cardiovascular mortality in subjects with depression at baseline compared with subjects without depressive symptoms (Figure 2). Other epidemiologic studies of depression and cardiovascular disease show that depression remains a risk factor for the development of cardiovascular disease, after controlling for cardiovascular risk factors such as smoking, weight, cholesterol level, and family history.[9–14]

Depression post-MI is also associated with a high rate of cardiovascular mortality. This observation was first made in a sample of 222 consecutive patients evaluated at 5 to 15 days after MI and then followed up for 18 months.[15] Using a modified version of the National Institute of Mental Health Diagnostic Interview Schedule,[16] 16% of patients were identified as meeting DSM-III-R criteria for major depressive disorder. By 6 months post-MI, 17% of depressed patients had died owing to cardiovascular causes compared with 3% of nondepressed patients. The risk of increased cardiac mortality was not restricted to individuals who were classified with major depression. At 18 months post-MI, patients who did not fulfill the criteria for major depression but who did have Beck Depression Inventory scores greater than 10 had the same mortality rate as patients who had major depression (17%).[17] Intriguingly, those patients with ventricular premature depolarizations and high Beck scores had a mortality rate of around 50%.

TREATMENT OF DEPRESSION IN PATIENTS WITH CARDIOVASCULAR DISEASE

Given that there is accumulating evidence for a relationship between depressive illness and cardiovascular mortality, and data suggest that treatment of depression might reduce cardiovascular risk, it is necessary to consider the safety of antidepressant agents for patients with cardiovascular disease in order to identify effective and safe treatment options. The cardiovascular effects of tricy-

clic antidepressants (TCAs) are well characterized. Studies of therapeutic plasma levels of TCAs in depressed patients with and without cardiovascular disease have demonstrated that orthostatic hypotension is of major concern, particularly in the management of elderly patients, who are most susceptible to serious injury resulting from falls.[18] Of all the TCAs, nortriptyline carries the lowest risk of orthostatic hypotension.[19] Left ventricular function, even for patients with severe left ventricular impairment, does not appear to be routinely affected by TCAs. Tricyclic antidepressants similar to procainamide and quinidine have Type IA antiarrhythmic activity. These agents routinely slow cardiac conduction, recorded as increases in PR, QRS, and QTc intervals on the electrocardiogram. This effect is potentially fatal for patients with preexisting conduction problems, such as a bundle-branch block.

Until the early 1990s, when considering the treatment of a depressed patient with cardiac disease, the robust efficacy of TCAs as antidepressants, combined with the presumed potential for reducing the risk of cardiac mortality by treating depression, was weighed against the adverse cardiac effects of the TCAs (e.g., orthostatic hypotension, slowed cardiac conduction). However, the results of the Cardiac Arrhythmia Suppression Trial (CAST)[20] exposed serious implications for the use of TCAs in patients with ischemic heart disease. The CAST was designed to test the hypothesis that the use of antiarrhythmic agents in post-MI patients with ventricular irritability would increase survival. However, the results were, surprisingly, exactly opposite to the hypothesis: there was a significant increase in mortality of patients treated with the Type IC_a agents encainide and flecainide or the Type IA agent moricizine, compared with patients in the placebo group.[20,21] Since TCAs are also Type IA antiarrhythmic drugs, it should be assumed that they carry a similar risk in patients with ischemic heart disease. Moreover, the fact that ischemia is frequently the etiology of cardiac disease clearly affects

Table 1. Cardiac Status of Patients With Major Depression and Ischemic Heart Disease Treated With Paroxetine or Nortriptyline for 6 Weeks[a]

| Variable	Paroxetine (N = 41)	Nortriptyline (N = 40)
Prior MI, %	61	73
History of angina, %	90	78
Prior CABG, %	37	35
Prior angioplasty, %	42	40
Ejection fraction, %	58 ± 14	60 ± 14

[a]Data from Roose et al.[23] Abbreviations: CABG = coronary artery bypass graft surgery, MI = myocardial infarction.

the risk/benefit ratio for the use of TCAs in depressed patients with cardiovascular disease.

The effectiveness and generally favorable adverse effect profile of the selective serotonin (5-hydroxytryptamine) reuptake inhibitors (SSRIs) are now well established in the treatment of depression. Furthermore, data are now available to assess whether the SSRIs are a safe alternative to TCAs in the treatment of patients with depression and cardiovascular disease. The first study to specifically consider the safety of SSRIs for the treatment of concomitant depression and cardiovascular disease was an open study of fluoxetine in 27 patients with DSM-III-R criteria for major depression, Hamilton Rating Scale for Depression (HAM-D) score ≥ 16, and heart failure and/or conduction disease and/ or ventricular arrhythmias.[22] Forty-five percent of the patients in this study had a history of previous MI. After 7 weeks of treatment at a dose of up to 60 mg/day the SSRI had no effect on blood pressure, cardiac conduction, or ventricular ectopic activity but did induce a statistically significant decrease in heart rate of 5 beats/min. No patients withdrew owing to adverse cardiac events.

One prospective, randomized, controlled study[23] has compared treatment with the SSRI paroxetine with a therapeutic plasma level of the TCA nortriptyline in depressed patients with ischemic heart disease. In this study, 81 patients with unipolar depression and significant but stable ischemic heart disease were randomly assigned to receive either paroxetine (up to 40 mg/day) or nortriptyline doses to achieve a therapeutic plasma nortriptyline level of 80 to 120 ng/mL during a 6-week treatment period. Patients were excluded if they had experienced an MI within 3 months of entering the study. Two thirds of the patients had a history of MI prior to the 3-month exclusion period. Despite significant cardiovascular disease, patients were stable with a good cardiac output (mean ejection fraction = 59% by radionuclide angiography) (Table 1). Concomitant cardiovascular medication included β-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and nitrates. Paroxetine and nortriptyline were equally effective in the treatment of depression. A remission criterion of a final HAM-D score of ≤ 8 was achieved in 60% of paroxetine-treated patients and 55% of nortriptyline-treated patients (intent-to-treat analysis). The

Figure 3. Change in Heart Rate (beats per minute) in Patients With Major Depression and Ischemic Heart Disease Treated With Paroxetine or Nortriptyline for 6 Weeks[a]
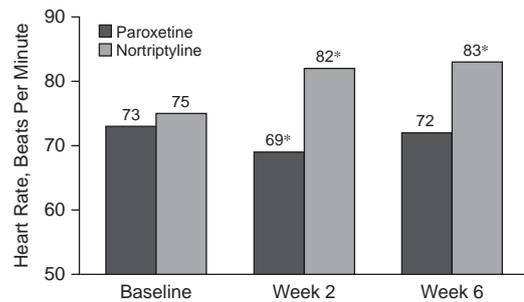
[a]Reprinted, with permission, from Roose et al.[23]
*p < .01 baseline versus week 2 or week 6.

adverse cardiovascular effects of the TCA nortriptyline were apparent over the 6-week treatment period. Specifically and predictably in nortriptyline-treated patients, there was an increase of 11% in mean heart rate (Figure 3), an increase in orthostatic drop, and a 50% reduction of ventricular premature depolarizations. Paroxetine did not cause any clinically significant, sustained changes in blood pressure, heart rate (see Figure 3), conduction intervals, or cardiac rhythm. Early withdrawals from the study due to documented, significant, adverse cardiac events (e.g., tachycardia) occurred in 7 patients taking nortriptyline compared with 1 patient receiving paroxetine.

An open-label pilot study known as the Sertraline Antidepressant Heart Attack Trial[24] was conducted to gather information on efficacy, safety, and cardiovascular responses to treatment with sertraline in patients with post-MI depression. Patients with major depression and ejection fraction > 35% were entered into the study 5 to 30 days post-MI. During the 16 weeks of treatment, sertraline (50–200 mg/day) had no effect on heart rate, blood pressure, cardiac conduction, or left ventricular ejection fraction. On the basis of these positive findings, a randomized, placebo-controlled study (the Sertraline Antidepressant Heart Attack Recovery Trial [SADHART]) has been initiated with a follow-up period of 18 months post-MI.

Therefore, studies have shown that, unlike the TCAs, the SSRIs have a benign cardiovascular profile. However, owing to the limited number of patients and cardiac conduction studies to date, it would be premature to conclude that SSRIs are safe for the treatment of all depressed patients with heart disease.

CONCLUSIONS

Treatment decisions for depressed patients with cardiovascular disease should be guided by knowledge of the cardiovascular effects of the available antidepressants. To date, studies of the SSRIs have shown a benign cardiovascular

profile and have emerged as a safer and effective alternative to the TCAs in depressed patients with ischemic heart disease.

Studies have shown that both major and subsyndromal depression are linked to an increased risk for the development of cardiovascular disease. This raises the question of how patients with comorbid depression and cardiovascular disease should be identified in the primary care setting and whether treatment of the depression can reduce the cardiac risk.

Depression in patients with already manifest cardiovascular disease is a significant risk factor for increased cardiac mortality. Therefore, management of depressed patients with a family history of cardiovascular disease and other cardiovascular risk factors, patients recently identified with CAD, and patients who are post-MI should be tailored to reducing cardiac risk. However, there are currently no data showing that treating depression can actually reduce cardiovascular mortality—the currently ongoing SADHART and Enhanced Recovery in Coronary Heart Disease, a cognitive-behavioral therapy trial, should provide some useful information on whether a pharmacologic or a psychotherapeutic intervention can reduce mortality.

Recent studies have hinted at the pathophysiologic mechanisms that may link depression with cardiovascular mortality. For example, increased platelet activity occurs in chronically depressed patients.[25] Therefore, having depression and an atherosclerotic disease may increase the likelihood for a platelet-induced ischemic event.[26] Alterations in the platelet serotonin system have been described in both conditions, and, interestingly, the SSRIs apparently can interfere with platelet activation. Pollock et al.[27] compared the effects of paroxetine and nortriptyline on platelet factor 4 and β-thyroglobulin, which were elevated at baseline in patients with depression and ischemic heart disease. While nortriptyline had no effect on platelet factors, paroxetine essentially normalized platelet factor levels. Depressed patients also have a decreased high frequency heart rate variability, indicating decreased parasympathetic tone. Thus, if a platelet-induced ischemic event occurs, it is more likely to generate ventricular fibrillation and consequent sudden death.[28]

The direction of further study into the most appropriate treatment of depression in cardiovascular disease will surely be guided by the results of the SADHART study and further understanding of the pathophysiology of platelet thrombosis and ventricular arrhythmias.

Drug names: flecainide (Tambocor), fluoxetine (Prozac), moricizine (Ethmozine), nortriptyline (Pamelor and others), paroxetine (Paxil), procainamide (Procanbid and others), quinidine (Quinidex and others).

REFERENCES

1. Carney RM, Rich MW, Tevelde A, et al. Major depressive disorder in coronary artery disease. Am J Cardiol 1987;60:1273–1275
2. Schleifer SJ, Macari-Hinson MM, Coyle DA, et al. The nature and course of depression following myocardial infarction. Arch Intern Med 1989;149:1785–1789
3. Carney RM, Rich MW, Freedland KE, et al. Major depressive disorder predicts cardiac events in patients with coronary artery disease. Psychosom Med 1988;50:627–633
4. Malzberg B. Mortality among patients with involution melancholia. Am J Psychiatry 1937;93:1231–1238
5. Black DW, Warrack G, Winokur G. The Iowa record-linkage study, 3: excess mortality among patients with "functional" disorders. Arch Gen Psychiatry 1985;42:82–88
6. Weeke A. Cause of death in manic-depressives. In: Schou M, Stromgren E, eds. Origin, Prevention and Treatment of Affective Disorders. London, England: Academic Press; 1979:289–299
7. Murphy JM, Monson RR, Olivier DC, et al. Affective disorders and mortality: a general population study. Arch Gen Psychiatry 1987;44:473–480
8. Rabins PV, Harvis K, Koven S. High fatality rates of late-life depression associated with cardiovascular disease. J Affect Disord 1985;9:165–167
9. Barefoot JC, Schroll M. Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. Circulation 1996;93:1976–1980
10. Aromaa A, Raitasalo R, Reunanen A, et al. Depression and cardiovascular diseases. Acta Psychiatr Scand Suppl 1994;377:77–82
11. Everson SA, Goldberg DE, Kaplan GA. Hopelessness and risk of mortality and incidence of myocardial infarction and cancer. Psychosom Med 1996;58:113–121
12. Pratt LA, Ford DE, Crum RM, et al. Depression, psychotropic medication, and risk of myocardial infarction: prospective data from the Baltimore ECA follow-up. Circulation 1996;94:3123–3129
13. Vogt T, Pope C, Mullooly J, et al. Mental health status as a predictor of morbidity and mortality: a 15-year follow-up of members of a health maintenance organization. Am J Public Health 1994;84:227–231
14. Ford DE, Mead LA, Chang PP, et al. Depression is a risk factor for coronary artery disease in men: the precursors study. Arch Intern Med 1998;158:1422–1426
15. Frasure-Smith N, Lespérance F, Talajic M. Depression following myocardial infarction: impact on 6-month survival. JAMA 1993;270:1819–1825
16. Robins LN, Helzer JE, Croughan J, et al. National Institute of Mental Health Diagnostic Interview Schedule. Arch Gen Psychiatry 1981;38:381–389
17. Frasure-Smith N, Lespérance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. Circulation 1995;91:999–1005
18. Roose SP, Glassman AH, Dalack GW. Depression, heart disease, and tricyclic antidepressants. J Clin Psychiatry 1989;50(7, suppl):12–18
19. Roose SP, Glassman AH, Siris SG, et al. Comparison of imipramine- and nortriptyline-induced hypotension: a meaningful difference. J Clin Psychopharmacol 1981;1:316–319
20. Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321:406–412
21. Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. N Engl J Med 1992;327:227–233
22. Roose SP, Glassman AH, Attia E, et al. Cardiovascular effects of fluoxetine in depressed patients with heart disease. Am J Psychiatry 1998;5:660–665
23. Roose SP, Laghrissi-Thode F, Kennedy JS, et al. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. JAMA 1998;279:287–291
24. Shapiro PA, Lespérance F, Frasure-Smith N, et al. An open-label preliminary trial of sertraline for treatment of major depression after acute myocardial infarction (the SADHAT Trial). Am Heart J 1999;137:1100–1106
25. Musselman DL, Tomer A, Manatunga AK, et al. Exaggerated platelet reactivity in major depression. Am J Psychiatry 1996;153:1313–1317
26. Laghrissi-Thode F, Wagner WR, Pollock BG, et al. Elevated platelet factor 4 and β-thromboglobulin plasma levels in depressed patients with ischemic heart disease. Biol Psychiatry 1997;42:290–295
27. Pollock BG, Laghrissi-Thode F, Wagner WR, et al. Increased platelet factor 4 and β-thyroglobulin in depressed patients with ischemic heart disease. Presented at the 34th annual meeting of the American College of Neuropsychopharmacology; Dec 11–14, 1995; San Juan, Puerto Rico
28. Sheps DS, Sheffield D. Depression, anxiety, and the cardiovascular system: the cardiologist's perspective. J Clin Psychiatry 2001;62(suppl 8):12–16